April 5, 1952

My dear Hayes:

I appreciate your courtesy in consulting me about your paper at the next SGM session. I was about to say that it was not really necessary, but I do not want to deprive myself of any opportunity of hearing from you. Of course you may quote our findings at length- and the experiments themselves, if you wish. I should mention that Cavalli is joined with Mrs. Lederberg and myself in a collaboration on this particular work, but I think any one of us can speak for the others. If I have managed to make myself clear about them, our interpretations are also available to you. Transduction is, I think, a useful word for infective types of genetic transmission. It is largely intended to supplant "transformation" [as in pneumococcus] which I find misleading.

I am not sure just what you mean by "confirming by genetic means the relevance of streptomycin in the sexual process itself." From your experiments, it would be a good guess that streptomycin (on S^s cells) does not inhibit cells from continuing with their F+ functions, but does inhibit them as F-. This can be confirmed, in part, by the definite (but very low) yields of W-S^r F+ x TL- S^s F+ [by transduction] on sm-minimal agar. The whole situation may be more complex than either you or I have imagined. The very low yield of this last cross leads me to wonder whether we don't have a system of relative potency, in which the lower partner, even in an F+ x F+, behaves as a relative F-. I'd rather not be quoted on this yet, but it looks as if this picture may yet work. Your suggestion (restated) that an F+ culture may show phenotypic variation so that some cells will behave momentarily as F- is equally sound (and perhaps supported by the effect of aeration in impressing such a behavior on 58-161), but it does not seem to fit so well. I am so much in the middle of thoughts and experiments on these points that I can't give you a very stable picture of the status of our speculations until they themselves settle down. To change the subject, we have been trying to cross sm-inactivated 58-161, washed to remove surplus sm, on to W-677, so far unsuccessfully. Have you tried this? The residual sm is not enough to inhibit the growth of added prototrophs, and we have the check of the occurrence of S^s prototrophs from 58-161 S^t x W-677 S^r. If this is really so, it makes a good argument for real zygotic fusion, for it means that the S^t "gamete" carries enough sm or sm-inhibited cytoplasm to inhibit further development of an S^s, but not a S^r, "ob-"gamete. It might also weaken the whole experiment, for one could argue that S^t cells are apparently sterilized only because of the persistence of the antibiotic. I would welcome your criticism of this point. I trust you will agree that the extruded-gamete concept is only one of several hypotheses, and note that your second letter to Nature abandons the proposal of the first that the gamete is lambda. Unfortunately (as I gloomily thought to myself) this hypothesis has been uncritically accepted, perhaps almost to the point of distortion, by various people (especially in Paris). Their feeling seems to be that your experiment conclusively throws out sexuality as an explanation of recombination in K-12. For my part, this is either quibbling or nonsense, but if I may have shown some signs of annoyance, please believe that they were not directed at you. If, as I believe, you stand with me on this issue, I hope you will take pains to express yourself in such a way that this kind of misunderstanding will be less likely to arise.

Cavalli has mentioned your wish to publish more fully in JGM, and I applaud the suggestion of a concomitant publication. Although I shall very much enjoy hearing from you directly, it may be more convenient for you to deal directly with Cavalli on this matter, as he will probably bear the main burden of writing, as senior author.

my work on the compatibility story, this point of view must be rejected. Just what it does mean, I am perhaps too chary of suggesting. A physiological differentiation of gametes is certain; whether there is a corresponding morphological differentiation (including your suggestion of the extrusion) is unsettled. I do not personally care for the terms "gene donor" and gene acceptor, because they carry a connotation of a transductive process. On the other hand, it now appears that the peculiar linkage behavior of filial stocks can be related to their polarity with respect to F+. There is a good deal of evidence that, following fertilization, there is an elimination of a chromosomal segment carrying the Mal and S, but none of the other factors so far recognized. This elimination also perturbs the segregation of other factors, such as Lac, V_1, etc. It would be possible to interpret this on the basis of a defective gamete, but I think it more likely from the regularity of this behavior, and from the constitution of persistent diploids, that the (relatively) F+ parent contributes a full genome, but that this genome later suffers the elimination of the Mal-S segment. [I have a chapter in Genetics in the 20th Century, MacMillan, 1951, that goes over some of the background on this. We now better understand what determines

the direction of elimination."

I can see no possibility that the F+ agent is itself the gamete, nor can it be lambda.

Perhaps I misunderstood your letter to Nature on the S^M crosses: do you suggest that streptomycin induces the extrusion of the gamete to the cell surface? If this were the case, S^t 58-161 should be more fertile than non-treated. Is this so? You will not have missed noticing that we are converging on a common viewpoint. While agglutination (Nat. Inst. Med. Res., at Mill Hill) published an acct. of a similar agglutination on the S^M crosses (which I had dismissed as an accident of E. segregation ratios or something of the sort), and of C. & differentiation completely yet suppose it would be worth trying to resuscitate the insight examination of these? Finally, do you know of any morphological studies I doubt if the cells lyse; do they do anything else?

Sincerely,